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A COMPARISON OF SOME EFFECTS OF THREE ANTIMOTION SICKNESS DRUGS--ETC(U)
AUG 81 W E COLLINS, D J SCHROEDER, G W ELAM

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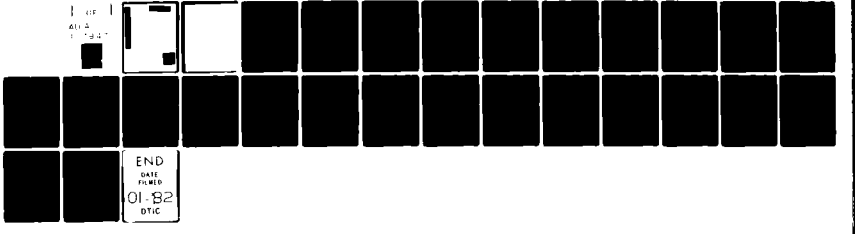

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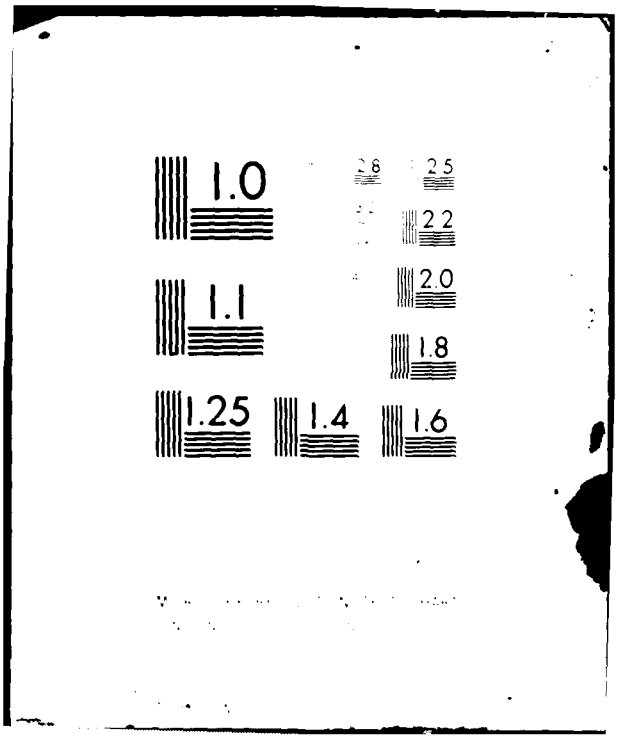
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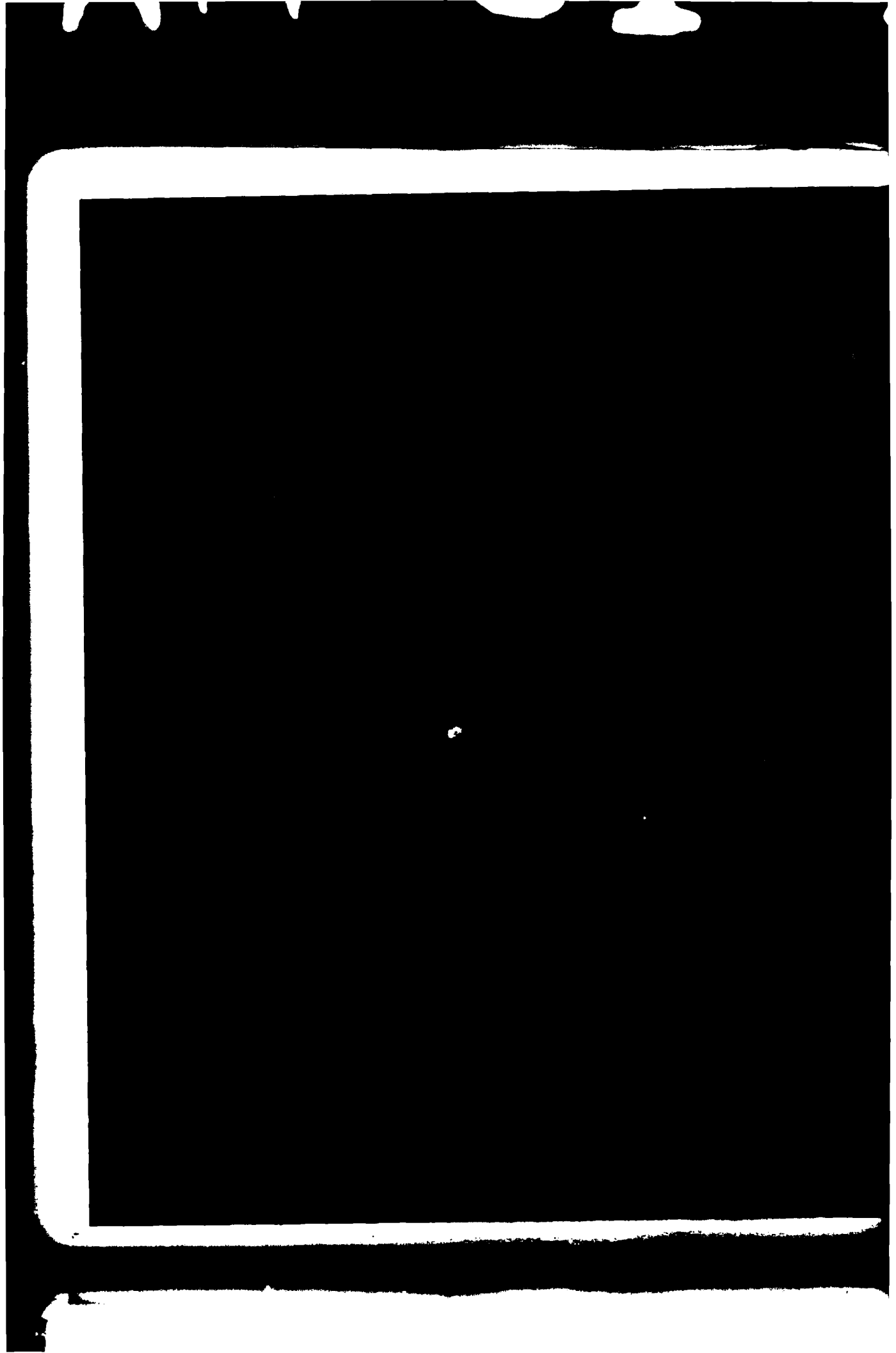

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16. Abstract

In aviation, some pilot trainees experience motion sickness early in their training and drug remedies are not prohibited when prescribed for dual flights. Moreover, some motion sickness preventives do not require prescriptions. In addition, spouses or business associates often accompany private pilots on flying trips: some of these passengers, who may be required to pilot the aircraft in an emergency, use antimotion sickness drugs. While the basic efficacy of such drugs is rooted in the reduction of motion sickness symptoms, adverse side effects are important practical considerations of their usage in aviation. This study examined the influence of three established antimotion sickness drugs on nystagmic eye movement responses to angular acceleration (whole-body movement) with vision either permitted or denied, and to optokinetic stimulation (visual field movement). Dimenhydrinate and promethazine hydrochloride, particularly at higher dose levels, reduced optokinetic nystagmus, thereby making less accurate the following ability of the eye. During whole-body motion in darkness, there was little placebo-drug difference in the vestibular response under alert conditions; under relaxed conditions, dimenhydrinate and promethazine hydrochloride produced significant declines in the vestibular eye movements. These same drugs also interfered with the ability of the individual to fixate adequately on a visual task during motion. Subjects who received a combination of promethazine plus d-amphetamine were able to suppress vestibular eye movements under the task condition and maintain good visual fixation. Thus, the effect of a drug on nystagmus may be a poor indicator of its value in preventing motion sickness. Moreover, assessments of antimotion sickness drugs for many practical situations should include as a possible adverse side effect the inability to maintain visual fixation during motion.

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A COMPARISON OF SOME EFFECTS OF THREE ANTIMOTION SICKNESS DRUGS ON NYSTAGMIC RESPONSES TO ANGULAR ACCELERATIONS AND TO OPTOKINETIC STIMULI

Introduction.

In aviation, some pilot trainees experience varying degrees of motion sickness early in their training and the use of drug remedies is not prohibited when prescribed for dual flights. Moreover, some motion sickness preventives do not require prescriptions. In addition, spouses or business executives often accompany private pilots on flying trips; some of these passengers, who may be required to pilot the aircraft in an emergency, use antimotion sickness drugs.

The majority of antimotion sickness drugs are depressants (2,11,12,17). While their efficacy in this regard is based on the reduction of motion sickness symptoms, there is the possibility that the use of such drugs might have other (undesirable) consequences on functions associated with motion, particularly with regard to the integrity of the visual and vestibular systems. Interferences with visual acuity, visual following ability, or the ability to maintain visual fixation during the nystagmic eye movement responses to angular accelerations all have potentially adverse consequences for spatial orientation and flight safety.

Among the factors which have a marked influence on vestibular nystagmus are the presence or absence of opportunities for visual fixation (6,8,10,14) and the state of mental alertness of the individual (1,4,5). Ordinarily, (i) the slow-phase components of vestibularly induced eye movements in darkness are reduced during states of mental relaxation (reverie) as compared with states of mental alertness, and (ii) nystagmic excursions are inhibited by visual fixation (6). Assessments of drug effects on vestibular responses--or on responses related to vestibular function--need to consider both of these factors. Several studies (1,9,10,14,15) have indicated that drug-induced alterations in the alertness of subjects might lead to inexact interpretations of the site of drug effects or to an incorrect appraisal of how a sensory system might perform under modified arousal conditions. For example, in one study (10), vestibular nystagmus in darkness was not differentially affected by ordinary doses of d-amphetamine sulphate (10 mg), secobarbital sodium (100 mg), or placebo if laboratory subjects were kept mentally alert during stimulation. If the subjects were allowed to relax and daydream, response variability increased markedly and the depressant, secobarbital sodium, produced a notable deterioration of the ocular response (10). Similar results were obtained with alcohol (14,15) and l-hyoscine hydrobromide (1). With vision permitted during vestibular stimulation, an opposite effect has been reported, viz, ocular nystagmus was increased by alcohol (14,15), amylobarbitone sodium (13), and secobarbital sodium (10).

The present study was designed to investigate the effects of three antimotion sickness drugs on the ocular nystagmus response to angular stimulation.

These tests were conducted under conditions in which (i) the subjects were made alert or were encouraged to relax and (ii) visual fixation was permitted or denied. Additional information was obtained by exposing the subjects to optokinetic stimulation. The drugs selected were (i) a readily available, nonprescription remedy, (dimenhydrinate), (ii) an antihistaminic (promethazine hydrochloride) which produces drowsiness (16), (iii) a combination of the antihistaminic (promethazine hydrochloride) with an analeptic (dextroamphetamine), the combination representing an exceptionally effective remedy for motion sickness (18).

Method.

Subjects. Male college students, with no history of any neuro-otological difficulties, served as paid subjects. None had any previous laboratory experiences involving vestibular stimulation. All ate a light breakfast at about 7:00 a.m. and were not allowed to smoke or drink beverages containing caffeine, except during a 2-h lunch period which preceded the final test session. In the first of two studies, 40 subjects were divided into four equal groups: a placebo (lactose), a 50 mg dimenhydrinate, a 25 mg promethazine hydrochloride, and a mixture (25 mg promethazine hydrochloride plus 10 mg d-amphetamine sulfate) group. The latter combination of drugs was included because it has been cited as one of the most effective antimotion sickness drugs in laboratory studies (17). In the second study (conducted to clarify some findings from Study I), 30 new subjects were divided into three equal groups: a placebo (lactose), a 100 mg dimenhydrinate and a 50 mg promethazine hydrochloride group. The drugs and placebo were placed in identical capsules; subjects were unaware of what their capsules contained.

Apparatus. A drum, painted with alternating black and white stripes (5 cm and 6.25 cm in width, respectively) was located 0.6 m in front of the subject to provide the optokinetic stimulation. The drum, 40 cm high and 50 cm in diameter, was mounted behind a gray screen which had a center opening the full size of the drum. Stimuli comprised 30-s periods of drum rotation at 10 rpm.

Vestibular stimulation was provided by oscillation of a modified Stille-Werner RS-3 rotation device. This enclosed device was programed to provide a triangular waveform stimulus with a 48-s period and reach a peak velocity of 120°/s in both counter-clockwise (CCW) and clockwise (CW) directions. Thus, each 48-s period produced a 24-s cycle of CW stimulation and a 24-s cycle of CCW stimulation, yielding cycles of both right-beating and left-beating nystagmus, respectively. Subjects were seated directly over the center of rotation with their heads fixed upright so that the lateral semicircular canals were approximately in the plane of rotation.

The nystagmic eye movements resulting from optokinetic and vestibular stimulation were recorded by using conventional electronystagmographic techniques. A Beckman Type T electroencephalograph, with a 3-s time constant, served as the recorder. Calibrations were obtained by having the subjects sweep their eyes between two flashing pinlights on the front of the rotator and between two markers near the optokinetic drum.

Procedure. During a single day, each subject was tested on five separate occasions: a familiarization session, a predrug (baseline) session, and three postdrug sessions. Immediately following the predrug session (between 10 a.m. and 11 a.m.), each subject ingested a capsule containing either one of the drugs or a lactose-placebo. The capsules were administered in a double-blind procedure. The postdrug sessions occurred 1, 2, and 4 hours following the ingestion of the capsule.

Each experimental session began with optokinetic stimulation; the stimulus period was 30 s and eye movements were recorded for an additional 30 s after the drum had stopped. The subject was periodically admonished to "stay alert" and to continue focusing on the surface of the drum. Pulse rates were recorded shortly after the end of the optokinetic trials.

The subject was taken next to a nearby room where the rotation device was located. Each rotation session involved (i) three periods of whole-body oscillation with the subject fixating visually and performing on a one-degree-of-freedom compensatory tracking task (alert with vision) and (ii) two periods of whole-body oscillation in total darkness under two alertness conditions. During the latter, the subjects were instructed either (i) to solve mental arithmetic problems assigned by the experimenter or (ii) to relax and daydream; i.e., assume a reverie (REV) state (4). The order of presentation of these latter two conditions was counterbalanced and, in both cases, the subject was instructed to keep his eyes open and look straight ahead.

Scoring. The total amount (degrees) of slow-phase eye displacement during vestibular stimulation was measured and the number of nystagmic eye movements (beats) was counted across the three periods of rotation in the light and across the first period of rotation in the dark. For optokinetic stimulation, like values were calculated on the 30-s stimulus period. Scoring was accomplished without knowledge of the group (drugs or placebo) to which any subject belonged, and these absolute values (or the differences between them) were used in the statistical analysis; for the latter, the minimal acceptable level for statistical significance was set at $p < .05$.

For some graphic presentations, however, "change" scores were computed. For each group and each measure, the mean score for the predrug session was plotted as a zero base; the percentages of increase or decrease in scores during subsequent sessions, which followed administration of a drug or placebo, were plotted as "percent increase" or "percent decrease" from the predrug level.

Results.

Pulse Rates.

STUDY I

For each group, analyses of variance followed by Tukey's Honestly Significant Difference (HSD) tests of pulse rates across sessions yielded

similar findings, viz, pulse rates were higher during the final sessions ($p < .05 - p < .001$) than they were during each previous session irrespective of drugs or placebo and, with one exception (the 2-h postdrug session for the mixture group), preingestion pulse rates were next highest (see Table 1). Analyses of difference scores showed no overall significant differences between groups, but there was a significant sessions effect ($p < .001$) due to the uniformly high pulse rates during the final session. Those high rates are probably attributable to the subjects' anticipation that the end of the experimental period was approaching. In any event, the presence or absence of drugs could not be ascertained by an inspection of pulse rates.

Table 1. Mean Pulse Rates Obtained During Each Predrug and Postdrug Session in Two Studies

Study I		Postdrug Sessions		
Group	Predrug	1 h	2 h	4 h
Dimenhydrinate (50 mg)	68.7	62.8	62.0	77.9
Mixture (*)	64.8	63.3	67.3	78.4
Placebo	64.2	60.9	61.4	71.1
Promethazine Hydrochloride (25 mg)	68.6	67.8	67.4	79.2
Mean	66.6	63.7	64.5	76.7
Study II				
Dimenhydrinate (100 mg)	71.3	64.0	63.0	76.4
Placebo	65.0	60.4	57.8	68.2
Promethazine Hydrochloride (50 mg)	65.8	60.2	60.8	69.4
Mean	67.4	61.5	60.5	71.3

(*) 25 mg promethazine hydrochloride plus 10 mg d-amphetamine sulphate.

STUDY II

Complementing the findings of Study I, pulse rates uniformly dropped for all groups during the first two postingestion sessions and reached their

highest levels during the final sessions for each group. Owing at least partly to the effects of the double dosages of drugs, the array of statistically significant findings differed between the two studies. Specifically, in Study II (i) the final session for each group had significantly higher ($p < .05 - p < .001$) pulse rates than the two preceding sessions but did not differ from the predrug session, (ii) placebo group scores during the 2-h session were lower ($p < .01$) than predrug pulse rates and (iii) pulse rates for the dimenhydrinate group were lower than baseline during both the 1-h and 2-h sessions ($p < .05$ in both cases). The overall analysis of difference scores yielded findings almost identical with those of Study I; there were no significant group differences but there was a session effect ($p < .001$) due to the elevated scores during the final sessions. Even with the increased drug dosages used in this study, pulse rates did not distinguish the presence or absence of the two depressant drugs.

Effects of Instructions.

STUDY I

Analyses of variance were applied separately to the slow-phase output and the number of eye movements (beats) elicited in darkness. The two different sets of instructions regarding mental activity yielded significant F-ratios for each ocular measure. For slow-phase displacement, instructions ($p < .01$), sessions ($p < .01$), and the instructions by sessions by groups interaction ($p < .05$) were significant; for the total number of eye movements, the same variables were significant ($p < .01$, $p < .05$, $p < .01$ respectively) plus the two-way interactions of sessions by groups and sessions by instructions (both at $p < .05$). For every session and every group, slow-phase measures for the mental arithmetic (MA) instructions were greater than those for the REV instructions (see Figure 1). The effect of instructions on the number of eye movements (Figure 2) showed different patterns, viz, (i) during the preingestion (baseline) sessions for all groups, the number of beats was greater for REV than for MA instructions, (ii) this pattern was maintained for both the placebo and mixture groups during subsequent sessions, and (iii) the REV output dropped below that of MA during two postingestion sessions each for the groups given dimenhydrinate (1-h and 2-h postdrug) and promethazine (2-h and 4-h postdrug).

Response trends across sessions were examined within each group via one-way analysis of variance and Tukey's HSD test. For the MA task, no significant effects were obtained for dimenhydrinate or promethazine. For the placebo group the number of eye movements was lower during the 1-h postingestion session than it was during all other sessions ($p < .05 - .01$). Somewhat similarly, the mixture group had less nystagmus output ($p < .05$) during the 1-h postingestion session than during the predrug session for both nystagmus measures; in addition, slow-phase scores during the 2-h session for the mixture group were lower ($p < .05$) than the predrug scores. REV sessions produced a different pattern of results.

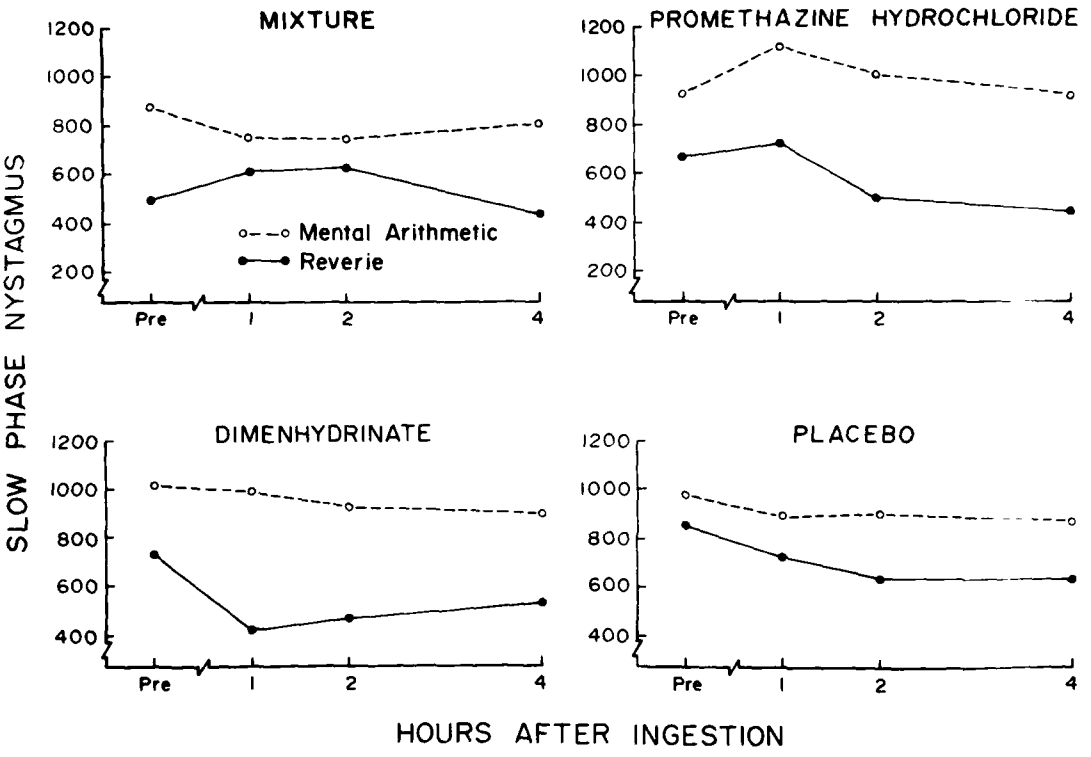

Figure 1. The total amount of slow-phase vestibular nystagmus obtained during rotation in total darkness under mental arithmetic and reverie instructions before (pre) and after ingestion of a drug or placebo. Drugs were dimenhydrinate (50 mg), promethazine hydrochloride (25 mg) and a mixture (25 mg promethazine hydrochloride plus 10 mg dextroamphetamine).

For this instructional condition, no significant effects were obtained for either the placebo or the mixture group. However, significant declines for both REV nystagmus measures ($p < .05$ in all cases) were present between the predrug and the 1-h postingestion session for the dimenhydrinate group and between the 1-h and 4-h postingestion sessions for the promethazine group.

Analyses of variance of difference scores (each postingestion score subtracted from the predrug score) and subsequent simple effects tests permitted assessment of difference between the groups. For the MA instructions, only one significant difference emerged, viz, for slow-phase activity during the first postingestion session between the mixture and promethazine groups ($p < .05$). The difference is attributable to the sharp increase in this

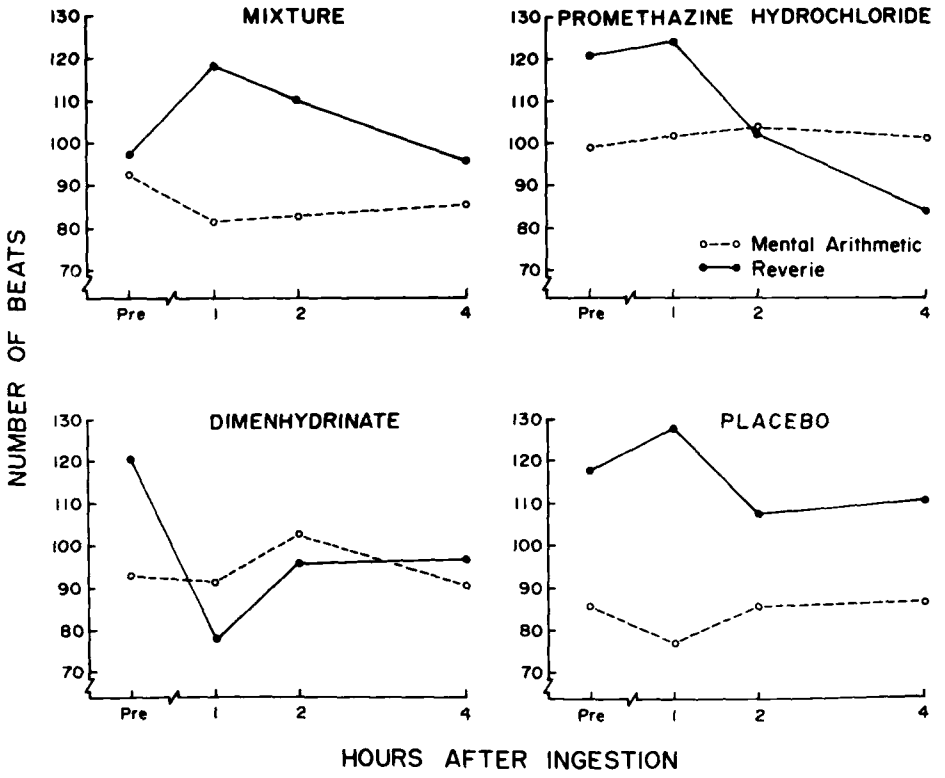

Figure 2. The total number of fast-phase beats of nystagmus obtained during rotation in total darkness before (pre) and after ingestion of a drug or placebo. Drugs and tasks were as in Figure 1.

measure of nystagmus for the promethazine group (see Figure 3). (This latter finding helped prompt the conduct of Study II.) REV instructions resulted in a greater number of significant effects ($p < .05$ in all cases), each of which involved depressed scores during the 1-h postingestion session for the dimenhydrinate group; specifically between the dimenhydrinate and mixture groups for both ocular measurements (Figures 3 and 4) and between the dimenhydrinate and placebo groups for the number of eye movements (Figure 4).

STUDY II

Analyses of variance applied to the two measures of nystagmus yielded almost identical patterns of significant F-ratios. For both measures, instructions ($p < .01$), session ($p < .01$) and the groups by sessions ($p < .01$), instructions by sessions ($p < .01$), and three-way interactions ($p < .01$) were all significant. The groups by instructions interaction was significant ($p < .05$) only for the number of ocular beats. Slow-phase output for every session and every group was greater for MA than for REV

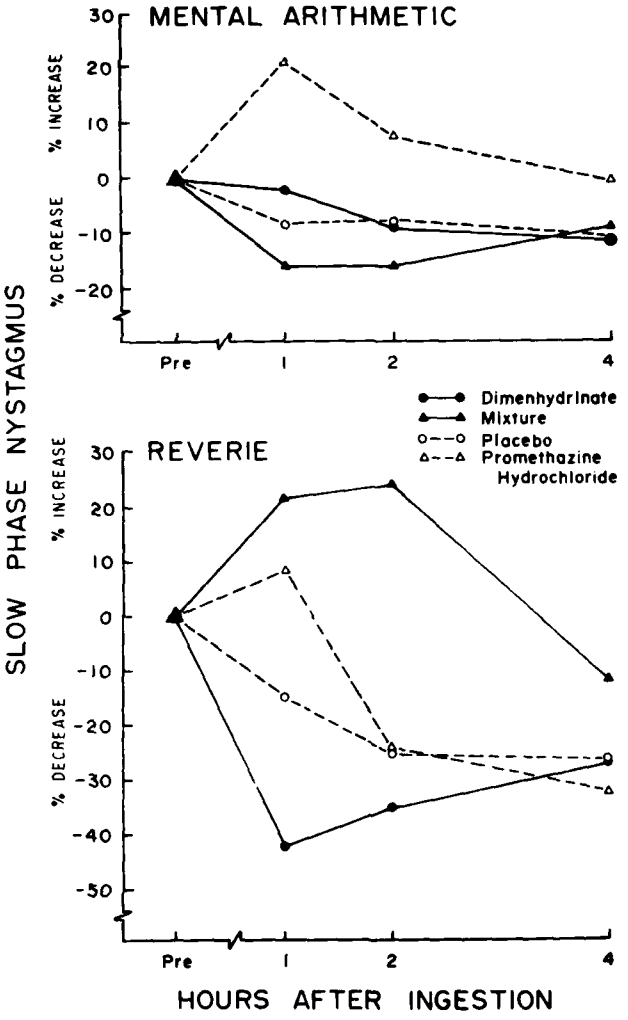

Figure 3. Changes in the output of slow-phase vestibular nystagmus following ingestion of a drug or placebo. Drugs and tasks were as in Figure 1. The 0 scores represent the base levels of ocular output for the four groups under mental arithmetic and reverie instructions; output scores for the postingestion sessions were converted to percentages of increase or decrease from the base levels.

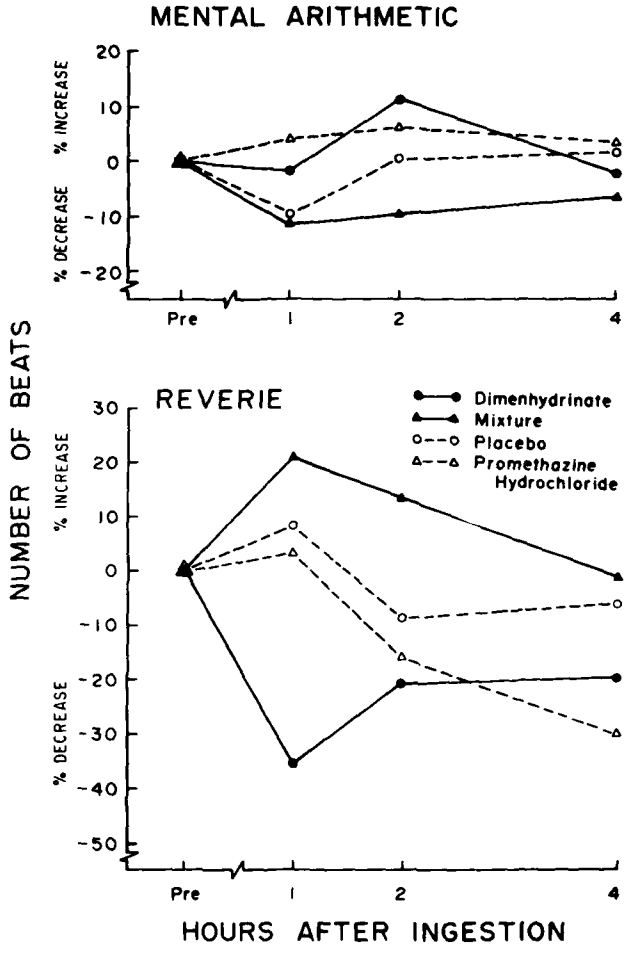

Figure 4. Changes in the total number of fast-phase beats of vestibular nystagmus following ingestion of a drug or placebo. Drugs, tasks, and plotting procedures were as in Figure 3.

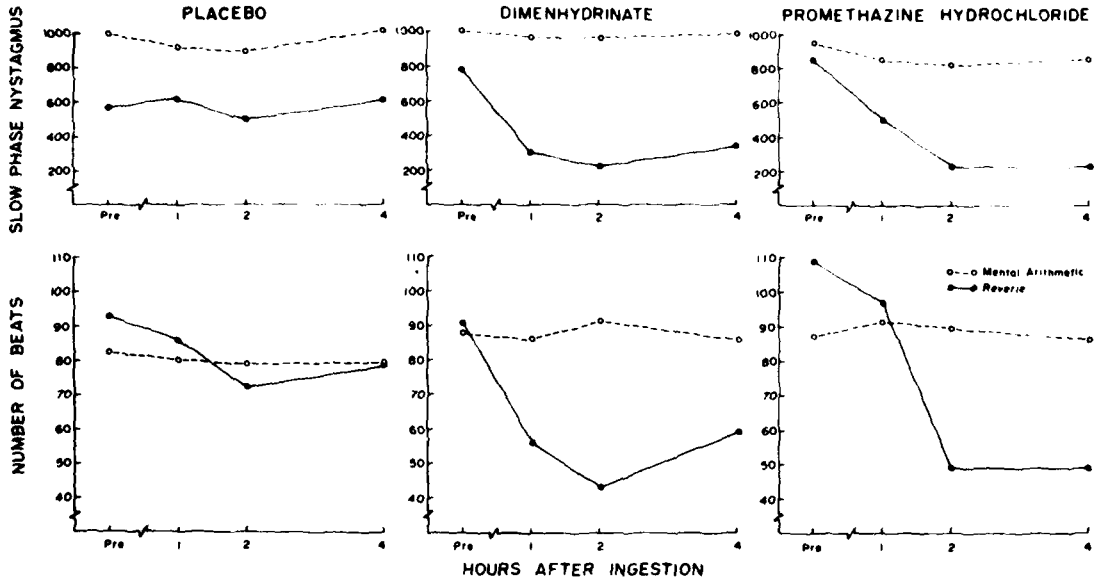

Figure 5. The total amount of slow-phase and fast-phase (number of beats) vestibular nystagmus obtained during rotation in total darkness under mental arithmetic and reverie instructions before (pre) and after ingestion of a drug or placebo. Dosages were 100 mg of dimenhydrinate or 50 mg of promethazine hydrochloride.

instructions; also the differences in output between the instructions grew clearly greater during postingestion sessions for dimenhydrinate and promethazine (see Figure 5). For the number of eye movements, all preingestion sessions showed higher scores during REV than during MA. This difference declined during postingestion sessions for the placebo group, but the scores stayed within ±10 percent of each other. For both promethazine and dimenhydrinate, sharp declines in ocular beats occurred during postingestion sessions, with REV scores markedly below MA scores during all three postingestion sessions for dimenhydrinate and during the last two sessions for promethazine.

In examining response trends across sessions for each group, the MA condition yielded significant F-ratios only for slow-phase measures (Figure 6), only for the 2-h postingestion session, and only for the placebo and promethazine groups, viz, for the former group, that session differed (scores were lower) from the predrug and the 4-h postingestion sessions ($p < .05$ in both cases), while for promethazine subjects the 2-h session (with a lower score) differed only from the predrug trial ($p < .05$). Although these differences were significant, the sessional range of scores was quite narrow (see Figure 6). Intersession comparisons for the REV instruction condition resulted in no significant F-ratios for the placebo group. However, dimenhydrinate produced marked postingestion declines in both measures of nystagmus (Figures 6 and 7), with all postingestion scores lower than the predrug levels ($p < .01 - .001$). Promethazine also produced sharp declines in each of the two measures of ocular activity, viz, all postingestion sessions were depressed from the predrug level for slow-phase scores, and all except the 1-h session were significantly depressed for the number of eye movements ($p < .001$ in all cases). In addition, the 1-h promethazine postingestion session differed significantly from the last two sessions (they were lower) for both nystagmus measures ($p < .05$ and .01 respectively for slow-phase; $p < .001$ in both cases for number of eye movements).

Analyses of variance of difference scores and subsequent simple effects tests to assess between-groups differences yielded none for the MA instructions (see Figures 6 and 7). REV instructions resulted in the following significant findings: (i) for all three postingestion sessions, slow-phase scores (Figure 6) for both drug groups showed a significantly greater drop ($p < .01 - .001$) from predrug levels than did the placebo group, (ii) for the number of ocular beats (Figure 7), promethazine scores dropped significantly more than placebo scores for the 2-h ($p < .05$) and the 4-h ($p < .01$) postingestion sessions.

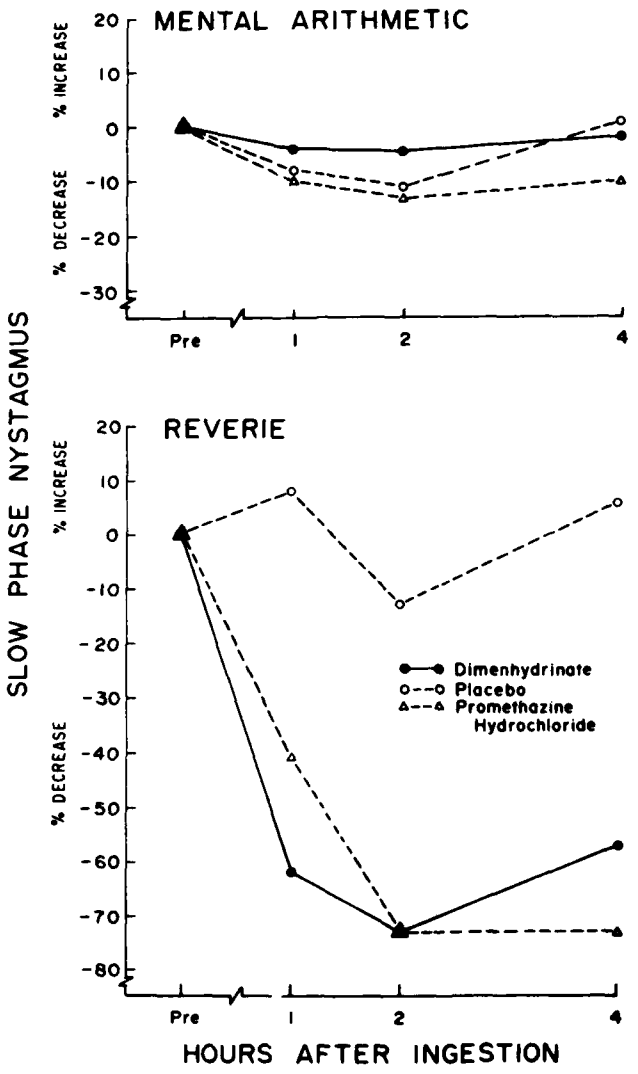

Figure 6. Changes in the output of slow-phase vestibular nystagmus following ingestion of a drug or placebo. Dosages and tasks were as in Figure 5. The 0 scores represent the base levels of ocular output for the four groups; output scores for the postingestion sessions were converted to percentages of increase or decrease from the base levels.

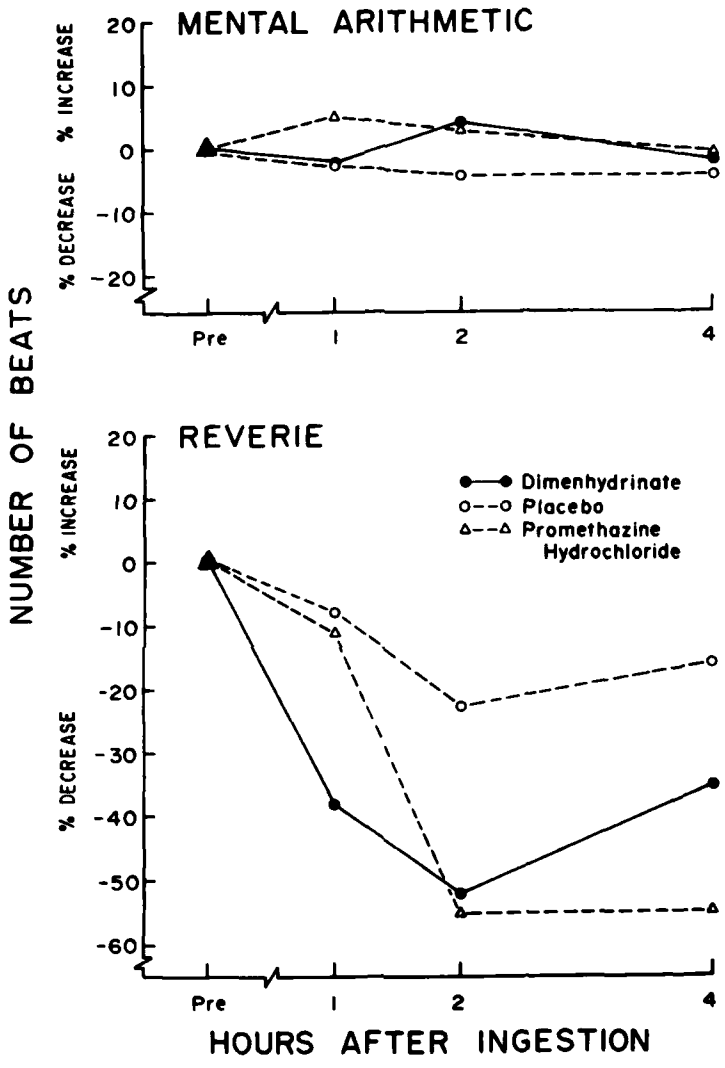

Figure 7. Changes in the total number of fast-phase beats of vestibular nystagmus following ingestion of a drug or placebo. Dosages, tasks, and plotting procedures were as in Figure 6.

Effects of Visual Fixation on Vestibular Nystagmus.

STUDY I

Within Groups Comparisons. One-way analyses of variance and Tukey's HSD tests yielded significant F-ratios for both the slow-phase and the number of beats measures for the placebo ($p < .05$) and mixture ($p < .01$) groups. Dimenhydrinate had no statistically significant effect across the four sessions but all postdrug scores exceeded the baseline levels. Promethazine produced a significant overall F($p < .05$) only for slow-phase scores (due to the elevated output 2-h after taking the drug), but all the paired-session comparisons fell short of statistical reliability.

The placebo group showed a general decline in nystagmus across sessions with both slow-phase displacement measures and the number of eye movements during the final session falling significantly below ($p < .01$) baseline levels. The mixture group declined more sharply than did the placebo subjects, but showed some recovery during the final session. For ocular beats, only the 2-h postingestion session for mixture subjects was significantly below the predrug level ($p < .01$), but for slow-phase measures all three postingestion sessions were lower than the baseline ($p < .01$, $p < .001$, and $p < .01$, respectively).

Thus both the placebo and mixture groups showed improved control of eye movements (lower scores) across sessions, while the subjects given dimenhydrinate and promethazine had elevated scores (reduced ocular control) after drug-taking.

Between Groups Comparisons. The overall analyses of variance and subsequent simple effects tests yielded significant findings for groups ($p < .01 - .001$) for each of the two ocular measures, and a significant groups-by-sessions interaction for the number of eye movements ($p < .05$). For the latter measure, the only group difference occurred during the 2-h postingestion session between the promethazine (high score) and mixture (low score) groups ($p < .001$). For slow-phase measures, the mixture group had less displacement than both the dimenhydrinate and promethazine groups during the 2-h ($p < .01$ and $p < .001$, respectively) and the 4-h sessions ($p < .01$ and $p < .05$, respectively). In addition, the promethazine group scores were higher ($p < .05$) than the placebo group scores during the second postingestion session.

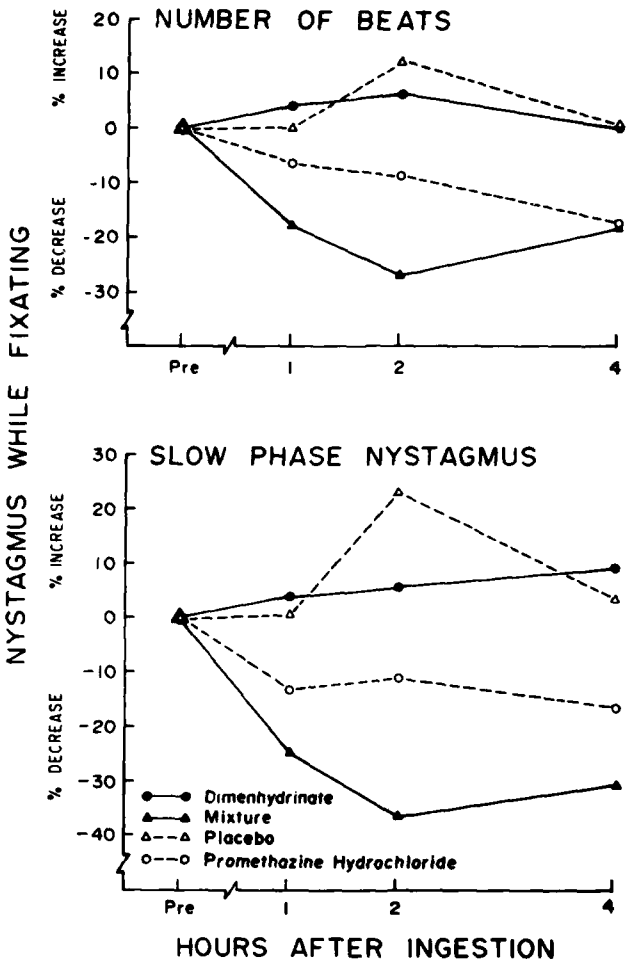

Figure 8. Changes in slow-phase and fast-phase (number of beats) vestibular nystagmus during visual fixation on a tracking task. Drugs were dimenhydrinate (50 mg), promethazine hydrochloride (25 mg) and a mixture (25 mg promethazine hydrochloride plus 10 mg dextroamphetamine). The 0 scores represent the base levels of ocular output for the four groups; output scores for the postingestion sessions were converted to percentages of increase or decrease from the base levels.

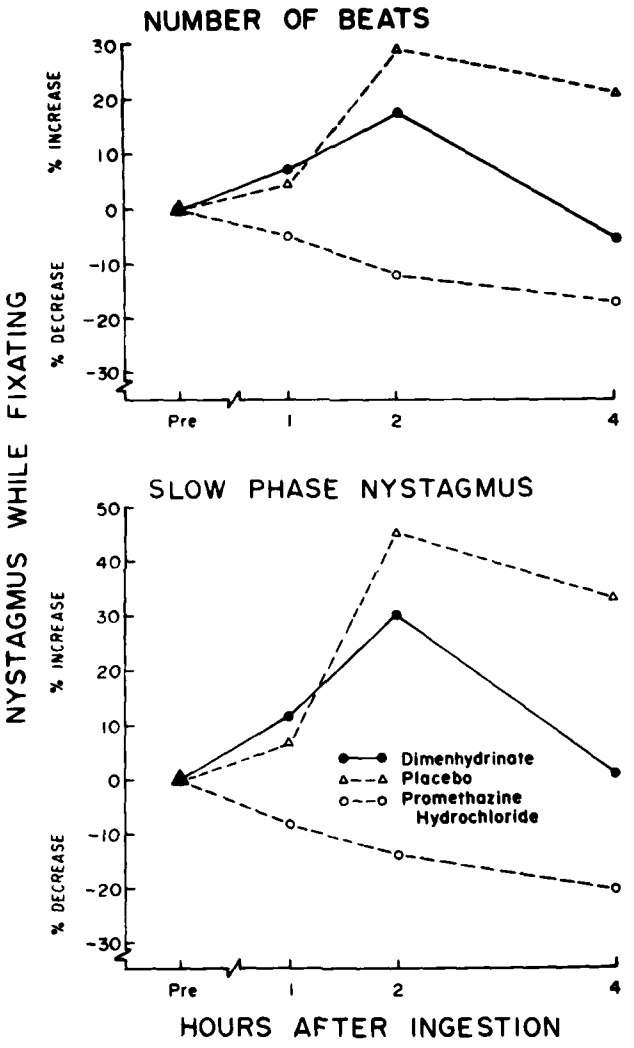

Figure 9. Changes in slow-phase and fast-phase (number of beats) vestibular nystagmus during visual fixation on a tracking task. Dosages were 100 mg of dimenhydrinate or 50 mg of promethazine hydrochloride. Plotting procedures were as in Figure 8.

STUDY II

Within Groups Comparisons. One-way analyses of variance yielded significant effects across sessions for both measures of nystagmus for the placebo ($p < .01$) and promethazine ($p < .05$) groups; for dimenhydrinate subjects, only the number of eye movements varied significantly ($p < .05$). Tukey's HSD tests yielded no sessional differences for dimenhydrinate although scores were elevated during the first two postingestion hours and several comparisons involving the second postingestion hour were very near statistical significance. For both measures of nystagmus, promethazine produced significantly higher scores ($p < .05$) during the second postingestion hour than prior to drug-taking and two other comparisons involving the 2-h postingestion session were close to significance. The last session for the placebo group was significantly lower ($p < .01$) in output than the first session for both measures of nystagmus, culminating a regular decline in eye movement (improved control) across sessions.

Between Groups Comparisons. Analyses of variance yielded significant F-ratios for groups ($p < .01$), sessions ($p < .05$), and for the groups by sessions interactions ($p < .05$ for slow phase and $p < .01$ for number of movements). For both measures dimenhydrinate ($p < .05$) and promethazine ($p < .001$) scores were significantly higher (less control) than placebo scores during the 2-h postingestion session. Promethazine scores remained significantly elevated during the last session in comparison with placebo ($p < .01$ for slow-phase and $p < .001$ for ocular beats) and were higher than dimenhydrinate scores ($p < .05$) during that session only for the number of eye movements.

Optokinetic Nystagmus.

STUDY I

Within Groups Comparisons. One-way analyses of variance across sessions for each group yielded no significant F-ratios for either slow-phase measures or the number of beats. While slow-phase scores generally declined across sessions, all scores were within ± 10 percent of the preingestion levels. Beats of eye movement were somewhat more stable across sessions and showed a narrower range of variability from predrug scores (Figure 10).

Between Groups Comparisons. Overall analyses of variance for the total number of optokinetic eye movements yielded no significant F-ratios; total slow-phase output yielded only a significant sessions effect ($p < .05$) which is accounted for primarily by the somewhat lower scores which occurred during the last two sessions. Individual comparisons between the groups at each session yielded no significant effects although, for number of beats, the promethazine-dimenhydrinate groups differences at the 1-h and 2-h postingestion sessions, and the promethazine-mixture group differences at the last session, all approached significance.

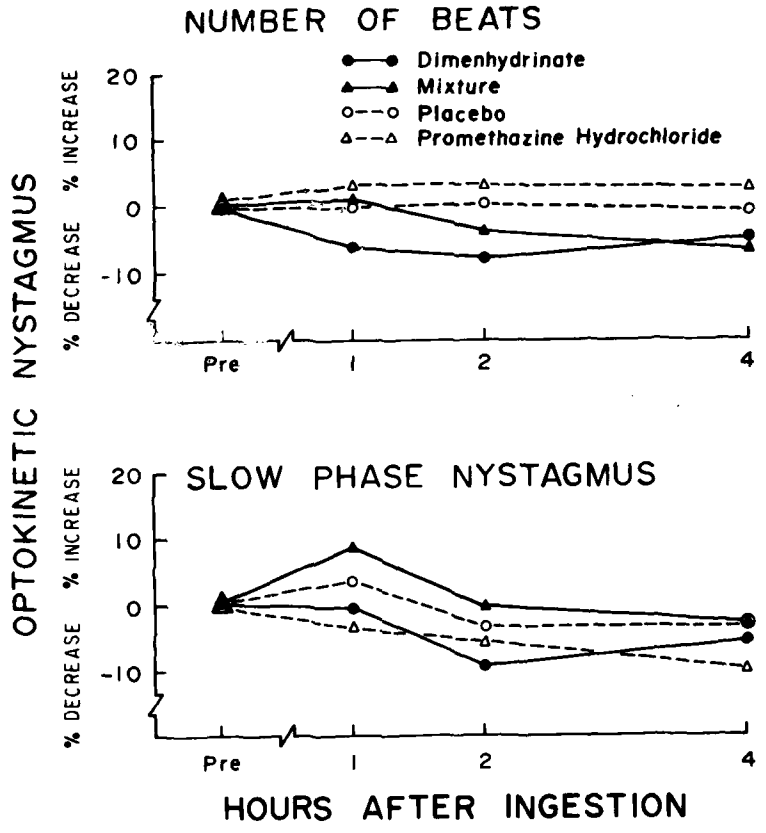

Figure 10. Changes in the output of optokinetic nystagmus obtained before (pre) and after ingestion of a drug or placebo. Drugs were dimenhydrinate (50 mg), promethazine hydrochloride (25 mg), and a mixture (25 mg promethazine hydrochloride plus 10 mg dextroamphetamine). The 0 scores represent the base levels of ocular output for the four groups; output scores for the postingestion sessions were converted to percentages of increase or decrease from the base levels.

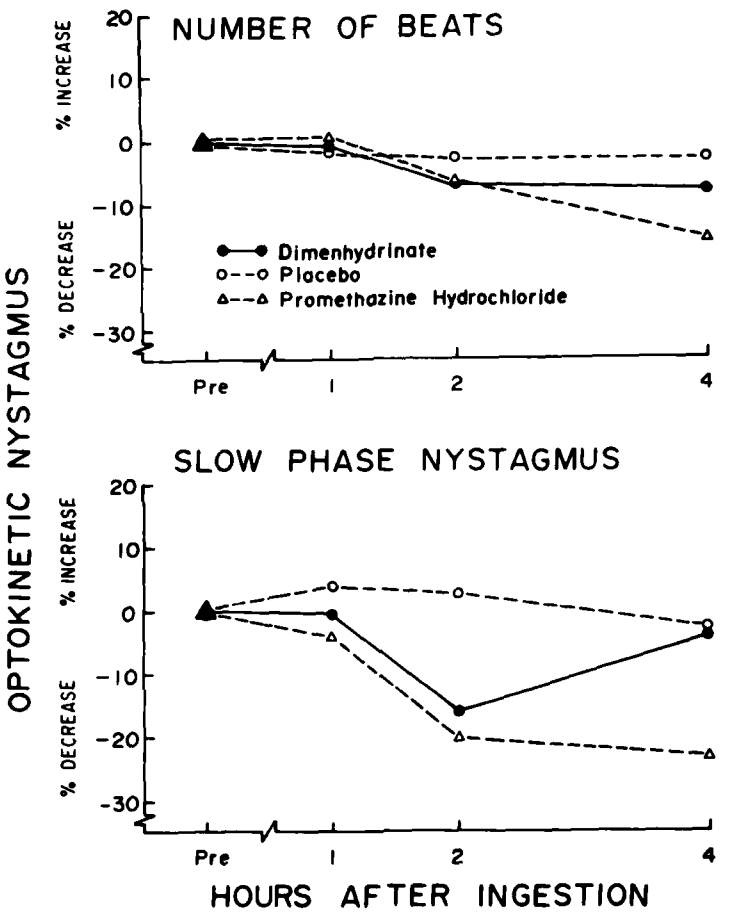

Figure 11. Changes in the output of optokinetic nystagmus obtained before (pre) and after ingestion of a drug or placebo. Dosages were 100 mg of dimenhydrinate or 50 mg of promethazine hydrochloride. Plotting procedures were as in Figure 10.

STUDY II

Within Groups Comparisons. One-way analyses of variance across sessions yielded significant effects only for the promethazine group. Comparisons between trials indicated that the last promethazine session had significantly less output for both measures of nystagmus than either the predrug ($p < .01$ in both cases) or the 1-h postingestion session ($p < .05 - .01$); in addition, for slow-phase activity, the 2-h session was significantly below ($p < .01$) the predrug level. Slow-phase displacement scores for the 2-h session also approached significance for the dimenhydrinate group; the slow-phase decline during this session fell short of the $p < .05$ level in comparisons with both the predrug and the 1-h postingestion sessions.

Between Groups Comparisons. Overall analyses of variance for total slow-phase output and for total number of eye movements yielded identical patterns of significance, viz, for sessions ($p < .01$) and for the groups by sessions interaction ($p < .01$). Both effects are due primarily to the variable (and depressed) scores of the promethazine and dimenhydrinate groups during the last two sessions as compared with the relatively stable scores of the placebo group (Figure 11).

Discussion.

The MA instructions tended to produce relatively stable session-to-session scores for slow-phase nystagmus regardless of the drug or dosage used in these two studies. For every session, the slow-phase output for MA trials exceeded the levels for REV instructions. REV resulted in more variability of slow-phase responses across sessions, particularly for promethazine and dimenhydrinate, and more variability for the double dosages than for the single ones.

Counts of the number of eye movements yielded mixed results. Again MA instructions produced relatively stable scores across sessions and the REV condition yielded greater trial-to-trial variability. However, the number of eye movements during each predrug session was consistently greater for the REV condition than for MA instructions. This difference in output favoring REV persisted across all sessions for the placebo and mixture groups in Study I, but was not maintained during the last two sessions for the placebo group in Study II. The most marked changes occurred in the dimenhydrinate and promethazine groups. The former evidenced a sharp decline in output 1-h postdrug; that decline (to levels below those of the MA condition) showed recovery during the final two sessions in Study I, but deepened during the 2-h session of Study II (under the double dosage) before some recovery was evident. For promethazine the sharp drop did not occur until the 2-h session in both studies and no recovery was apparent during the final sessions. These differences are, of course, related to the different time courses of peak action and duration of the drugs and their dosages.

Thus, the MA task effectively cancelled drug effects and stabilized the nystagmic response across trials irrespective of the drug administered. REV instructions permitted the depressant drugs (particularly at the higher dose levels) to affect nystagmus by means of an accelerated reduction in the response output across sessions. The mixture, which combined an analeptic (d-amphetamine) with one of the depressants (promethazine), had effects on nystagmus that were more like the effects of a placebo.

The present findings regarding mental set are similar to those of a previous study which assessed effects of secobarbital and of d-amphetamine on the same nystagmus parameters (10). In that study the MA and REV instructions produced about the same effects as were obtained in the present report on both slow-phase and fast-phase measures of nystagmus. The effects of secobarbital were more like the double dosages of dimenhydrinate and promethazine in terms of the magnitude of the decline during REV, while the effects of d-amphetamine resembled those of the mixture group in the present study.

Vestibular nystagmus during visual fixation yielded clear and consistent effects of drugs. In both Study I and Study II, nystagmus increased (i.e., visual control of vestibular eye movements decreased) during the first 2 hours after ingestion of dimenhydrinate or promethazine and, at best, during the final session, nystagmus output was back to the predrug level. Moreover, the increase in nystagmus was clearly greater for groups given the double dosages. The placebo group and the mixture group showed a different pattern of nystagmus activity, with general decline in output evident across all sessions. The declines suggest improved control of vestibular eye movements by means of visual fixation. Similar but less marked results were evident for the involuntary ocular following movements generated by optokinetic stimulation. Optokinetic effects were clearer for the double dosages which reduced both the speed of the following movements (reflected in less slow-phase displacement) and the frequency of fast-phases (smaller number of beats) thereby increasing the discrepancy between the speed of the moving object and the speed of the eye. It is of more than passing interest that the mixture group showed none of these negative effects.

These results and others (1,8,10,13,14,15) suggest that moderate dosages of depressant drugs have effects on vestibular nystagmus that are different depending upon the presence or absence of vision and the mental set of the subject. With respect to the latter, the instructional set assumed by the subject during vestibular testing appears to be one of the most important variables in determining overall slow-phase nystagmic output. In the present study, the alert set (mental arithmetic) prevented the response declines that were evident under the nonalert set (reverie) for the promethazine and dimenhydrinate groups. If alertness is not controlled, what may appear to be a drug-induced alteration in the responses might be simply a drug-induced alteration in the alertness of the subjects; such a difference may have considerable practical as well as theoretical significance. In the absence of instructions regarding arousal it is likely that subjects under

the influence of such drugs would drift into reverie-like states and thereby show reduced vestibular nystagmus. It is of interest that in the present study and in a previous one (10), the initial effect of REV instructions was to decrease the slow-phase activity but increase the number of fast-phase beats of nystagmus in darkness. With repetition of the REV condition (which, one might assume, would increase the ability to relax and daydream), the fast-phase activity also begins to fall off and such declines are accelerated by depressant drugs. It would appear that both the eye-centering reflex and the vestibularly induced slow-phase displacement mechanism are generally suppressed during a fairly complete state of mental relaxation. However, the two components do not seem to be equally responsive to the introduction of the REV state since at least the frequency of the fast-phase activity is not only initially reduced, but may show temporarily increased activity.

With respect to the influence of vision on nystagmus, both depressant drugs reduced the involuntary (optokinetic) following ability of the eye (with the higher dosage) as well as the ability of an individual to suppress vestibularly induced eye movements through visual fixation (with both dose levels). These may be important modifications in practical situation involving visual judgments about moving objects in the one case; and, in the other, in preventing blurred vision during motion. Of significance in this regard is that the combination of d-amphetamine sulphate and promethazine produced none of these undesirable consequences. In fact, the nystagmic responses obtained from the mixture group in the present study appear very much like those obtained in earlier studies (9,10) from subjects who were given d-amphetamine sulphate alone. Thus, although the central action of drugs that are effective in reducing malaise due to motion are still not clearly defined (3,11,12), the mixture combination has distinct advantages as a motion sickness preventive, viz, it has a high degree of efficacy in reducing or preventing undesirable motion sickness symptoms without ocular disadvantages that seem to be manifested by depressants alone. Other similar combinations (e.g., scopolomine plus amphetamine (11,18), scopolomine plus ephedrin (11,17), and promethazine plus ephedrin (11,18)), which also have proven highly effective as antimotion sickness preparations, are likely to have this same advantage.

The available data also suggest that the effects of a drug on vestibular nystagmus may be a poor indicator of its value in preventing motion sickness. Alcohol (14,15) and secobarbital (10), neither of which has any documented usefulness as a motion sickness preventive, produce effects on vestibular responses that are not unlike those of the 100-mg dose of dimenhydrinate or the 50-mg dose of promethazine, both of which provide a reasonable degree of protection against motion sickness (16). Moveover, assessments of the capacity of drugs to combat motion sickness in many practical situations should include as a possible adverse side effect the inability to maintain visual fixation during motion.

Summary.

While the basic efficacy of an antimotion sickness drug is rooted in the reduction of motion sickness symptoms, sites of drug action and adverse side effects are among the theoretical and practical considerations of drug usage in transportation systems. This study examined the influence of three established antimotion sickness drugs on nystagmic eye movement responses (i) to angular acceleration (whole-body movement) under conditions of mental alertness or relaxation and with vision either permitted or denied, and (ii) to optokinetic stimulation (visual field movement). Dimenhydrinate and promethazine, particularly at higher dose levels, reduced optokinetic nystagmus, thereby making less accurate the following ability of the eye. During whole-body motion in darkness, there was little evidence of any placebo-drug differences in the vestibular response under alert conditions; however, under relaxed conditions, dimenhydrinate and promethazine produced significant declines in the vestibular eye movement measures. With vision permitted during angular acceleration, these same drugs also interfered with the ability of the individual to fixate adequately on a visual task. Subjects who received a combination drug (promethazine plus d-amphetamine) responded much like placebo subjects under the visual task condition, demonstrating an ability to suppress vestibular eye movements and thereby maintain good visual fixation on a task. Thus, the effect of a drug on vestibular or optokinetic nystagmus may be a poor indicator of its value in preventing motion sickness. Moreover, assessment of the efficacy of drugs to combat motion sickness in many practical situations should include as a possible adverse side effect the inability to maintain visual fixation during motion.

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